International Journal of Basic and Applied Virology 4(2): 60-70, 2015
ISSN 2222-1298

DOI: 10.5829/idosi.ijbav.2015.4.2.95273

Review on Rabies, with Emphasis on Disease Control and Eradication Measures

Eyob Abera, Ashenafi Assefa, Shiret Belete and Natnael Mekonen

Department of Clinical Medicine, University of Gondar, P.O. Box: 196 Gondar, Ethiopia

Abstract: Rabies remains the most important zoonotic disease in many countries. Public concern and fears are most focused on dogs as the source of rabies infection to humans and other domestic animals. Several bat species are reservoir hosts of rabies and therefore can be a public health hazard. The possibility of a carrier state or asymptomatic form of rabies deserves serious evaluation. Rabies in most countries was successfully controlled through mass vaccination of dogs, long before the recognition of bat and other wildlife rabies and the availability of modern vaccines. Prompt and state of the art diagnostic tests that are field-based and introduction of efficient national programs are crucial for the successful control and eradication of rabies. A better understanding of the relationship between humans and dogs is a prerequisite for the implementation of more effective strategies for rabies control programmes. Adequate and appropriate strategies which are based on "One Health" approach are necessary in order to implement efficient control and eradication measures against rabies endemic, especially in developing countries.

Key words: Control · Eradication · Rabies · Mass vaccination · Zoonotic disease

INTRODUCTION

Rabies is a viral infectious disease of mammals including humans, characterized by the development of severe nervous symptoms that lead to paralysis and death. Once symptoms of the disease develop, rabies is invariably fatal. The disease affects domestic and wild animals and is spread to humans through close contact with infectious material, usually via bites or scratches. Rabies is present on all continents of the world with the exception of the Antarctica; however, more than 95% of human deaths due to the disease occur in Asia and Africa. Rabies infection in humans is still a major public health Problem all over the world. Rabies kills an estimated 35,000 per year, mostly in Africa, Asia and Latin America. It is a viral disease of CNS leading to Death of affected animal in most cases. Rabies is mainly a disease of animals. It is also a disease of all warm blooded animals [1].

Rabies is a viral zoonosis caused by negative-stranded RNA viruses from the Lyssavirus genus. Genetic variants of the genotype 1 Lyssavirus (The cause of classical rabies) are maintained in different parts of the world by different reservoir hosts within 'Host-adaptive landscapes' [1]. Although rabies can infect and be transmitted by a wide range of mammals, reservoirs comprise only mammalian species within the Orders Carnivora (Dogs, raccoons, skunks, foxes, jackals) and Chiroptera (Bats). From the perspective of human rabies, the vast majority of human cases (90%) results from the bites of rabid domestic dogs [2] and occur in regions where domestic dogs are the principal maintenance host [3].

Border control is the primary prevention measure to keep a rabies-free region away from rabies emergence. Canine rabies has been eradicated in Taiwan since 1961 because of the efforts on animal quarantine, large-scale vaccination and stray animal control. However, until now, canine rabies is still considered to be one of the most important threats to Taiwan. Over the past three decades, there have been marked differences in efforts to control canine rabies. Recent successes have been demonstrated in many parts of central and South America, where canine rabies has been brought under control through large-scale, synchronized mass dog vaccination campaigns [4]. As a result, not only has dog rabies declined, but human rabies deaths have also been eliminated, or cases remain highly localized [5]. The

Corresponding Author: Shiret Belete, Department of Clinical Medicine, University of Gondar, P.O. Box: 196 Gondar, Ethiopia.

contrast with the situation in Africa and Asia is striking; here, the incidence of dog rabies and human rabies deaths continue to escalate and new outbreaks have been occurring in areas previously free of the disease (e.g. the islands of Flores and Bali in Indonesia [6]. Successful elimination of human rabies has been demonstrated in many countries, including in developing countries such as the Philippines, Mexico and Indonesia. In the Philippines, a rabies elimination programme was launched in 2007 involving mass dog vaccination, dog population control, improved dog bite management, public education and improved diagnosis surveillance and monitoring. Within three years, human deaths due to rabies were reduced from eight persons per million to zero. Similar control efforts are underway in the southeastern part of the United Republic of Tanzania and Kwa-Zulu Natal in South Africa [7]. The aim of this Seminar is to review available information on rabies, including the causative lyssaviruses and disease transmission, management and prevention.

The objectives of this strategy will therefore be:

- To discuss on the epidemiology, transmission, pathology, clinical manifestations, diagnosis, treatment and control of rabies infectio
- To discuss on the recent strategies which is important to implement efficient control and eradication measures against rabies.

Definition of Rabies: Rabies originated about 3000 B.C from the word 'rabha' meaning violence. Rabies is one of the most typical zoonosis that has been well known since ages and has been known for more than 4300 years [8]. Rabies is a public health problem of significant importance in the majority of Southern and Eastern Mediterranean and Middle Eastern countries. In some of these countries, there is a considerable death rate due to rabies. Since 1912 when rabies was first confirmed in Kenya, the disease has largely existed in varied degrees of occurrence. Spatial and temporal distributions of cases of animal rabies are well documented [9]. The rabies problem in Kenya has been greatest in Machakos district where the disease has persisted endemically for over 40 years. Rabies is an acute encephalitis illness caused by rabies virus. Rabies virus is the prototype species of the genus Lyssavirus in the family of Rhabdoviridae. The virus affects virtually all mammals and infected species invariably die from the disease once clinical signs are manifested. Rabies is endemic in developing countries of Africa and Asia and most human deaths from the disease occur in these endemic countries. Rabies is one of the most deadly infectious diseases, with a case-fatality rate approaching 100%.

Epidemiology

Agent: The causes of rabies are RNA viruses belonging to the genus lyssavirus within the family Rhabdoviridae, order Mononegavirales. Rabies virus (RABV) is the type species and is responsible for most cases in human beings and animals [10]. However, cases of rabies involving human infection with the other lyssaviruses have also been reported and, from these cases, it seems most lyssaviruses cause indistinguishable fatal encephalitis in humans. Fatal cases of encephalitis caused by lyssavirus species other than RABV are extremely rare. However, surveillance capable of distinguishing different lyssaviruses in many endemic regions is not comprehensive [11].

Geographic Distribution: Rabies still remains a fatal infection in man and animals. It is found all over the world, except in some countries where there is strict quarantine system, rigorous eradication programme or natural barriers like mountains and rivers. Recently, the United States of America has been declared free of canine rabies [12]. By 1995, the world estimate deaths were about 70,000 humans per year, which are about 200 humans each day worldwide. However, there are only about 35,000 notifications per year [13].

Animal rabies ranked 12th in the WHO list of infectious and parasitic diseases that constitute the major causes of death [14]. It was also rated the 11th cause of human death due to infectious diseases in 2000 [15]. It has been reported that 98% of human rabies cases occurred in the developing countries of Asia, Africa and Latin America [16]. Many developed countries of the world have accurate reports on the outbreaks of rabies. In Nigeria, the status of rabies is unknown as reported by WHO [14], therefore rabies in animals and humans are grossly under-reported [17].

Reservoir: In Africa, evidence indicates that the primary rabies virus maintenance cycle is among domestic dogs, although other carnivores may be involved as non-maintenance populations [7].This finding suggests that mass vaccination targeting domestic dogs would have the greatest impact in reducing the risk of infection in all other

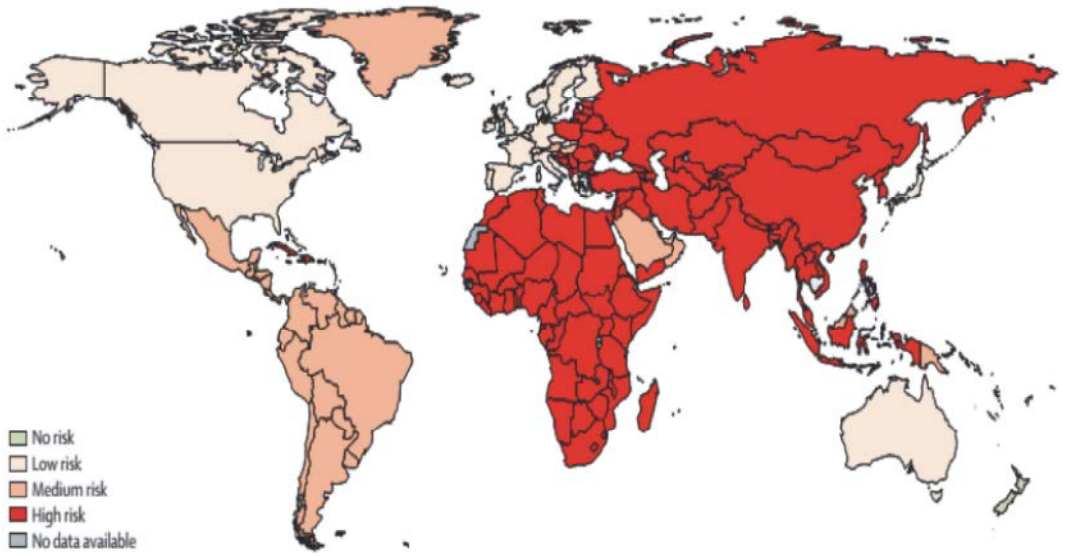

Fig. 1: WHO rabies risk map [14]

species including humans, livestock and wildlife [7]. In the Americas, bats are the source of most human rabies deaths while deaths following exposure foxes, raccoons, skunks, jackals, mongoose and other wild carnivores host species are rare. The role of bats and other carnivores in human rabies transmission in Africa appears minimal.

Transmission: Rabies virus is most commonly transmitted by the bite of a rabid animal. This mechanism enables the virus to transverse the dermal barrier and deposit the virus into tissues in which it can initiate infection. Hosts that do not contribute to onward transmission, including human beings, are termed dead end hosts. Transmission between human beings has only occurred in exceptional circumstances, including corneal and organ transplantation. Transmission of rabies virus by aerosol exposures or transplantation of tissues or organs is rare, but has been reported. Humans are usually infected following a bite or scratch by an infected animal. Transmission can also occur when infectious material – usually saliva – comes into direct contact with human mucosa or fresh skin wounds. Human-to-human transmission through bite is possible but rare. In rare cases, rabies may be contracted via transplantation of an infected organ. Ingestion of raw meat or other tissues from animals infected with rabies is not a source of human infection [18].

Pathogenesis: Once infection is established within neuronal cells the virus usurps host cell machinery to reach cell bodies in the spinal cord or brainstem or in sensory ganglia (e.g. dorsal root ganglia) where replication occurs. The motility of RABV along neuronal processes has been exploited to map neuronal circuitry [18]. The virus is transported by fast axonal transport through the spinal cord to the brain. Until this stage the patient shows no clinical signs. Once in the CNS, the virus replicates extensively and clinical disease develops. Notably, fatal encephalitic rabies might not necessarily be accompanied by substantial inflammation and this feature could, in part, be due to the genetics of the infecting virus. This variability in inflammatory response is also seen in cases of dog rabies [19].

- Virus enters muscle tissue of host through bite wound, then 2) enters the peripheral nervous system (PNS) via neuromuscular junction and then 3) travels from PNS to spinal cord and brain. 4) Virus enters brain and undergoes extensive replication leading to neuronal dysfunction (Slide shows virus in Purkinje cells of cerebellum 40 x magnifications). 5a) the virus replicates in salivary glands and is excreted in saliva, 5b) enters peripheral nerves of skin and Purkinje cells and 5c) spreads from the brain to infect many tissues and organs in the host.

Clinical Presentation

Incubation Period in Animals: The incubation period has been said to depend on the size of the viral inoculums, the proximity of the wound to large nerves and the length of the neural path from the wound to the brain [20]. Thus, it may be shorter following bites on the face and head and

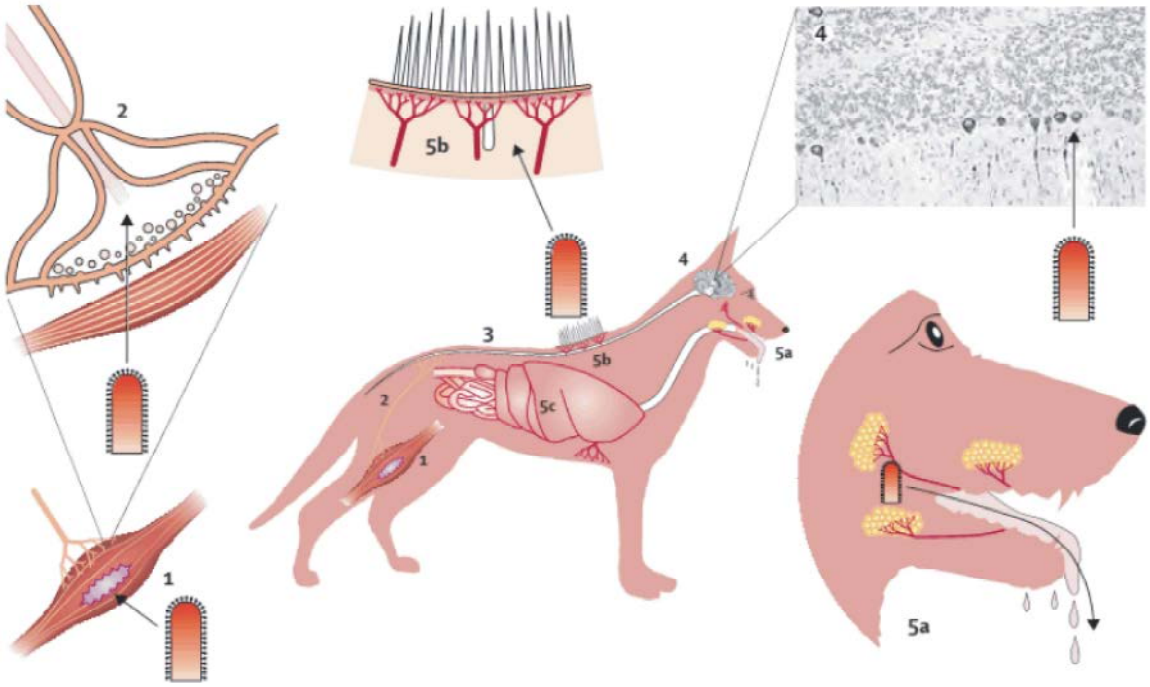

Fig. 2: Pathogenesis of rabies virus
(Source: Ugolini [19]

Fig. 3: Rabid dog [23]

longer when the bites occur in the legs or the extremities. It may also be shorter in small breeds of dogs as compared with large breeds [21]. The incubation period in animals can vary considerably. In dogs and cats, it is between 2 to 12 weeks, although longer incubation periods have been reported. Studies on the pathogenesis of rabies in the CNS have shown that clinical signs were not observed until after several growth cycles of the virus had occurred and the virus had spread through the entire CNS with the involvement of numerous neurons. The clinical signs may be variable in dogs at the onset but by the time the animal dies, there usually have been enough characteristic signs, evident of the disease.

Clinical Features in Animals: There are two distinct forms of rabies in animals, furious and dumb forms. Furious rabies is the classic "Mad-dog syndrome" and may be seen in all species. The animal becomes irritable and may viciously and aggressively use its teeth, claws, horns, or hooves to attack humans and other animals, without provocation. Such animals lose caution and fear of humans and other animals [22]. Dumb/paralytic rabies manifests with ataxia and paralysis of the throat and jaw muscles, often with profuse salivation and the inability to swallow. These animals may not be vicious. Rabid dogs or cats die within 10 days of onset symptoms [23].

Incubation Period in Humans: In humans, the incubation period for rabies is typically 1–3 months, but may vary from below 1 week to more than 1 year. The average incubation period of between 31 and 90 days has been reported, but it can be as short as 7 days, although it could be as long as 25 years [24]. Less than 1% of well documented cases had incubation periods of between 1 and 5 years following exposure [8]. The incubation period is usually between 20 and 90 days and it is shorter if the site of bites is on the head (25-40 days).

Clinical Features in Humans: The initial symptoms of rabies are fever and often pain or an unusual or unexplained tingling, pricking or burning sensation (Paraesthesia) at the wound site [10]. As the virus spreads through the central nervous system, progressive, fatal inflammation of the brain and spinal cord develops. Two forms of the disease can follow; furious or paralytic rabies. People with furious rabies exhibit signs of hyperactivity, excited behavior and hydrophobia (Fear of water) and death after a few days. Paralytic rabies accounts for about 30% of the total number of human cases. This form of rabies runs a less dramatic and usually longer course than the furious form. The muscles gradually become paralyzed, starting at the site of the bite or scratch. A coma slowly develops and death eventually occurs. The paralytic form of rabies is often misdiagnosed, contributing to the under-reporting of the disease. Once symptoms of the disease develop, the disease is fatal [25].

Diagnosis: Infection with rabies virus can be difficult to diagnose ante-mortem. Although hydrophobia is highly suggestive, no clinical signs of disease are pathognomonic for rabies. Historical reliance on the detection of accumulations of Negri-bodies is no longer regarded as suitable for diagnostic assessment because of low sensitivity and alternative laboratory-based tests have been developed to conclusively confirm infection [26]. Most diagnostic tests for rabies virus in animals need brain material for diagnosis and as such are often only possible post mortem [27]. Brain samples are most readily taken by breaching the skull and sampling directly. Brain smears or touch impressions are used for the detection of virus antigen with the fluorescent antibody test (FAT) for both human and animal samples. In animals: the direct fluorescent antibody test (dFAT) is the recommended diagnostic test [28]. This test detects the presence of rabies antigens in brain tissue. Other diagnostic techniques include reverse transcription polymerase chain reaction (RT-PCR), direct rapid immunohistochemistry test (dRIT) and serological tests (Fluorescent antibody neutralization test, rapid fluorescent focus inhibition test). In humans, the recommended test is dFAT on brain tissue. Other diagnostic tests that have been used are RT-PCR and dRIT [27].

Differential Diagnosis: Can involve many agents and syndromes (e.g. other viral encephalitides, tetanus, listeriosis and poisoning) and co-infections, such as malaria, can lead to misdiagnosis [26].

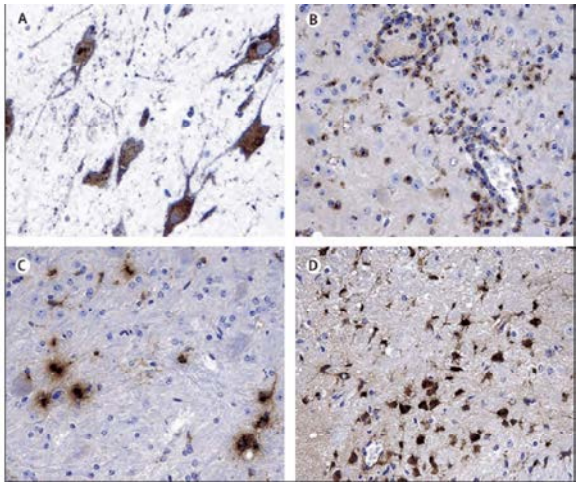

Fig. 4: Immunohistochemical detection of rabies virus nucleoprotein and chemokines in infected tissue. Immunohistochemical detection of rabies virus nucleoprotein (brown staining) in human neurons (a). Immunohistochemical staining for chemokines within the brain of mice infected with rabies virus (b-d). Magnification, ×200.
(Source: Fooks *et al*. [27]

Pathological Lesions

Gross Pathology: There are no pathognomic gross findings. Externally, there may be fresh or healed bite wounds and sometimes gross trauma due to self-mutilation. In areas with porcupines, quills may be found in the muzzle of affected animals. There may be an unusual odor, probably related to reduce hygiene in terminal disease. In the CNS there may be congestion of meningeal vessels, the brain tissue may appear pinker than usual and there may be mild cerebral edema [27].

Histopathology: Histopathological changes do not reflect the severity of the clinical disease. The general CNS findings are those of viral encephalitis, including Perivascular cuffing, vascular congestion, neuronophagia, neuronal degeneration and focal to diffuse gliosis. Lesions may be most severe in the brain stem. The presence of Negri bodies is considered pathognomic for rabies, but these are only seen in about 50 - 75% of cases. These are found most commonly in ganglionic cells of the hippocampus and in Purkinje cells of the cerebellum. Spongiform lesions may be found in the grey matter, in the neuropil and in neuronal cell bodies of the thalamus and cerebral cortex. Spinal and cranial nerve ganglia, particularly the Gasserian ganglia, may show an inflammatory response. There is no visible inflammatory response in the brain of some rabid individuals [29].

Morbidity and Mortality: It affects all warm-blooded animals [30] and having about 100% case-fatality rate. Human mortality due to rabies is estimated to be 50,000 deaths per year worldwide, mostly reported from Asia and Africa [30, 31] but it has worldwide public health importance [29]. If symptoms have appeared, the victim usually dies in spite of subsequent immunization and treatment with rabies immunoglobulin.

Recent Management, Control, Elimination and Prevention of Rabies: Rabies is a fatal disease in humans and, to date, the only survivors of the disease have received rabies vaccine before the onset of illness. The approach to management of the rabies normally should be palliative [32]. In unusual circumstances, a decision may be made to use an aggressive approach to therapy for patients who present at an early stage of clinical disease. According to Jackson *et al.* [32] no single therapeutic agent is likely to be effective, but a combination of specific therapies could be considered, including rabies vaccine, rabies immunoglobulin, monoclonal antibodies, ribavirin, interferon-alpha and ketamine. Corticosteroids should not be used. As research advances, new agents may become available in the future for the treatment of human rabies [32].

Rabies has the highest case-to-fatality ratio of any infectious disease and no spontaneous recoveries are reported. With rare exception, comfort care, sedation and life support measures may prolong life, but do not prevent death. Thus, in most situations, use of the term treatment is a misnomer and usually refers to medical aid related to animal bite and disease prevention by post exposure prophylaxis [1]. More than 12 million humans annually are exposed and may undergo anti-rabies prophylaxis, but in excess of an estimated 50,000 to 100,000 die, primarily from the bite of an infected dog. Public health expenditures have been poorly quantified. To date, no effective medical therapy has been established for overt rabies. The rabies post-exposure prophylaxis (PEP), which is a serial vaccination against rabies starting as soon as possible after the patient was bitten by a suspected rabid animal, is the only way to prevent death [8]. WHO recommends immediate washing of the wound with soap and water, application of human anti-rabies immunoglobulin and administration of tissue-culture rabies vaccine at 0, 3, 7, 14, 30 and 90 days after exposure [8].

Human diploid-cell vaccine and rabies vaccine adsorbed, which stimulate the production of antibodies and human rabies immune globulin, which provides protective antibodies, are nearly 100% effective in preventing progression from stage I disease. If left untreated, rabies is usually fatal. However, treatment with human diploid cell vaccine or rabies vaccine adsorbed and with human rabies immune globulin is nearly always curative if initiated early in the incubation period [33]. Preventive and control measures include exposure of vaccinated animal, immediate vaccination, quarantine and investigation for 10 days. Exposed unvaccinated animal should be euthanizing immediately. In human, First Aid should be given and a medical doctor should be consulted immediately. Other control methods include: vaccination, quarantine, pounding and killing stray dogs, wildlife around should be killed during an epidemic, wild animals should not be kept as pets and then oral vaccines should be given to wild animals through bait. Modern cell culture-based inactivated rabies virus vaccines have been used in control programs [34].

Management: Medical care of patients with rabies is challenging for all physicians, especially in regions where there is little experience of the disease or the complex treatment issues [32]. Critical care should be used as required pending Confirmation of a laboratory diagnosis of rabies and when an aggressive approach is deemed necessary, although the chance of a successful outcome is very low. Unfortunately, no effective therapy exists for rabies after the development of clinical disease. Clinical management of rabies has included a combination of therapies, rabies vaccine, immunotherapies and ketamine. Excellent medical care in a critical care unit is important, but no specific therapeutic drug is known to affect a positive outcome [32].

Control of Rabies in Animals: Rabies is not considered a serious candidate for disease eradication at this time because of numerous and diverse wild reservoirs [13]. The correlation between canine rabies and human fatalities, however, has led to the successful application of domestic animal vaccines, particularly in developed countries [35]. A comprehensive domestic animal program also requires responsible pet ownership. Such a program entails stray animal management; leash law amendments; humane population curtailment (e.g., early spay and neuter programs); animal importation, translocation and quarantine regulations; schedules for early pre exposure vaccination of companion animals (In light of potential maternal immune inhibition) and rational post exposure management [13]. Unlike post exposure prophylaxis of humans, euthanasia is usually recommended for the naive animal exposed to rabies, but this may eventually change with the development of safe and effective biological and protocols [35]. Current veterinary vaccines are more

potent than earlier attenuated and inactivated vaccines [35]. Because no vaccine is 100% effective, given poor cross-reactivity with some genotypes [36] and because correct identification of the properly immunized animal may be confusing, the vaccinated dog or cat is not exempt from confinement and close observation. This strict period of observation of the biting animal applies to dogs, cats and, in some countries, domestic ferrets [13]. In addition, pet vaccination status does not necessarily alter the need for euthanasia of an offending animal, regardless of vaccine potency or efficacy, if rabies is suspected [35].

Rabies Control Technology: Oral rabies vaccination (ORV), trap-vaccinate-release (TVR) and point infection control (PIC) are an evolving rabies control technologies for use in wildlife [37]. ORV involves distribution of baits containing orally immunogenic vaccines onto the landscape, thereby targeting wildlife to establish population immunity and prevent spread or eliminate specific rabies variants [37]. The first use of ORV sought to control rabies in red foxes (Vulpes vulpes) in Switzerland; subsequent programs were reported throughout much of Western Europe [39]. Switzerland, France, Belgium and Luxembourg were deemed free of the red fox variant by 2001 [38]. ORV of wildlife has had positive public health effects. Multiyear campaigns have led to progressive elimination of arctic fox-variant and canine-variant rabies in Ontario and Texas, respectively [37]. Trap vaccinate-release (TVR), point infection control (PIC) and ORV zones have prevented raccoon-variant rabies from becoming established in Ontario [37].

Current Rabies Control Activities: Rabies control in animals is under the mandate of the DVS and various methods have been put in place to control the disease. Limited dog vaccinations and issuance of certificates is conducted by the SCVOs. Dog vaccinations are also conducted by private Animal Health Service Provider (AHSPs) at a fee and by animal welfare organizations. However these efforts are largely uncoordinated and disjointed and have minimal impact on rabies control. There are also ongoing activities to raise public awareness on rabies in humans and animals and to provide information and advice on how to prevent the disease. The climax of public awareness and free dog vaccination against rabies is held during the World Rabies Day celebrations, an annual event held on 28th September every year. This brings together all stakeholders to share various efforts, achievements, research and way forward in rabies control. There are also efforts to control dog populations through neutering. This is carried out by the private and public veterinarians. Stray dog populations are also eliminated by culling usually conducted by the SCVOs. However, these efforts are minimal and have little impact on rabies elimination. In Humans, the MOH through the Unit of Vaccines and Immunization Services (UVIS) provides limited anti-rabies vaccines to health facilities and is in the process of developing guidelines on the management of dog bites and administration of PET [11].

Challenges of Rabies Control in East Africa: - There are a number of challenges in the prevention and control of rabies in East Africa as listed below:

Inadequate Laboratory Capacity: Human rabies diagnosis and management is largely dependent on diagnosis of rabid animals. Countrywide, there are only three animal laboratories that have the capacity to confirm rabies in humans or animals. However, these laboratories often lack reagents for timely testing of specimens. At the grass root level, there are inadequate resources for sample collection, packaging and shipping to diagnostic laboratories. There are no public health laboratories which carry out human rabies diagnosis [11]

Inadequate Surveillance: In the IDSR system, dog bites are used as a proxy for suspect rabies cases in humans. However, dog bites are under-reported in health facilities resulting in missed cases and misclassification of deaths due to rabies. There is underreporting of suspected rabies cases in dogs and other livestock due to the passive nature of the surveillance system. There is inadequate sharing of surveillance data between the human and animal health sectors at both local and national levels, often resulting in loss of opportunities to prevent human rabies, early detection and timely response to rabies outbreak. The national surveillance data is unreliable, meaning that the true burden of the disease in the country or high risk areas remains undefined; making it difficult to target prevention and control measures [34].

Inadequate Inter-Sectoral Collaboration and Partnerships: There is little coordination and collaboration between the human and animal health sectors and other agencies responsible for rabies control. Most of the rabies control and prevention activities in the country have been ad hoc, uncoordinated (Carried out by line ministries, NGOs, private practitioners) and without well-defined objectives or evaluation of progress (e.g. vaccination coverage, goals and indicators to measure success and the costs of these control activities) [11].

Low Awareness on Rabies Prevention and Control: There is low awareness among the public, human and animal health workers on management of dog bite wounds and pre- and post-exposure prophylaxis. Most patients who die from rabies are either misdiagnosed or do not receive timely and appropriate post-exposure treatment. In particular, many dog bites in children are not reported and may go completely unrecognized or be discovered late by both parents and health care providers. Knowledge of the benefits of responsible dog ownership and dog population management among the public is low. In addition, there is little understanding among the public of the value of timely response following dog bites and the value of timely PET. Compliance with completion of PEP regimens is low. Factors affecting PEP compliance of patients are not well known. There is low awareness among policy makers on the importance and burden of rabies and the cost-effectiveness of rabies control through dog vaccination [37].

Inadequate Enforcement of Laws and Regulations: Whereas there is adequate legislation requiring mandatory registration, licensing and vaccination of dogs and cats against rabies and responsible dog ownership, there is inadequate implementation and enforcement of the law. There are also county laws on responsible animal ownership that are not adhered to. This laxity in enforcement has resulted in a large population of unvaccinated dogs. Another weakness in legislation is that the rabies act applies only to designated rabies control areas, which are supposed to be gazetted. At the moment there are no gazette rabies control areas [37].

Inadequate Research on Rabies: There is inadequate research that can enhance rabies control. Data on important topics such as the economic benefits of rabies control, dog demographics and ecology and alternative dog population management methods is lacking [34].

Limited Supply of Anti-Rabies Vaccine: There is limited supply of animal rabies vaccine in the animal sector and also inadequate PET and PEP biologics in public health. Whereas these biologics may be available in private facilities, the cost is prohibitive. The possibilities for locally producing rabies vaccines have not been explored but never implemented [11].

Funding Constraints: Rabies control activities, particularly dog vaccination, are underfunded by the government. Most of the ad hoc rabies control activities are confined to small areas and dependent on unreliable donor support, resulting in little impact on rabies control [11].

Strategies for Rabies Elimination: he following strategies will be deployed in the rabies elimination plan.

Elimination of Rabies in Dogs: To conduct mass dog vaccination targeting greater than 70% of dog population coverage annually for three consecutive years; Dog population management comprising education, legislation, registration, sterilization, holding facilities, euthanasia and vaccinations and controlling access to garbage and left over's [16].

Prevention of Rabies in Humans: To provide timely access to appropriate Post Exposure Treatment (Wound cleaning, vaccination and rabies immunoglobulin) to all human cases of dog bites suspected to be rabid; To increase knowledge and skills among animal and human health workers on rabies in general and post-exposure management [31].

Strengthen Surveillance and Response to Outbreaks: To strengthen surveillance so that key indicators are routinely monitored and evaluated; to strengthen preparedness and response to rabies outbreaks [31].

Conduct and Promote Operational Research: Conduct and promote operational research to support implementation [16].

Advocacy, Communication and Social Mobilization: To increase community awareness and education on rabies prevention and control; to enhance community participation in rabies control activities [11].

Enhance Partnerships and Coordination: Strengthen capacity for planning, partnerships and coordination of the National Rabies Elimination Strategy; to strengthen capacity in program management in order to achieve rabies elimination objectives at all levels [31].

Resource Mobilization: To mobilize resources to support rabies elimination program; to invite interested development partners to participate and manage aspects of the project [16].

Cost Effectiveness of Rabies Elimination: The current efforts for rabies prevention and control in east Africa are restricted to human post exposure prophylaxis (PEP), voluntary and ad hoc dog vaccinations. This approach has not been successful in bringing down the cases of rabies in animals and humans, owing to inadequate vaccination coverage and unavailable or unaffordable PEP for most of the affected individuals [7]. There are three main strategies for the control of rabies; a) Prevention in man through intensified post-exposure treatment, b) Controlling the disease in the reservoir host; c) Combination of the two. To determine the most cost-effective method of the three studies have been conducted in Chad and Philippines. In the Philippines, cost–benefit analysis of mass dog vaccination versus human PEP over a six year period indicated that the use of intensified human PEP alone was associated with increasing medical costs to the government over the years in the absence of a dog vaccination program. In Chad, the cumulated cost of the combined strategy of human PEP and dog vaccination was found to be more efficient than the human PEP alone in the first 4 years and then was it became lower than human PEP cost after the 5th year of the program. The studies also showed that the cumulated cost of PET alone would be greater than the combined approach after the 6th year of elimination program [3]. Lessons from these studies show that continued rabies control using the current strategy (Ad hoc vaccinations without reaching the optimal 70%, supply of PEP to dog-bite victims) is less cost-effective compared to an elimination strategy that focuses on mass dog-vaccinations (Reaching the 70% vaccination coverage) accompanied by residual PEP for dog-bite victims. The economic benefit of mass dog vaccination and elimination of rabies in the animal reservoir will result from saving human lives, elimination of expenditures on human PEP and additional earnings and from livestock whose death is prevented [7].

Prevention of Rabies in Humans: Strategies for the prevention of human rabies are aimed at protecting those at highest risk of exposure, post exposure treatment and supportive management for the clinically ill. Specific activities will include

Early and appropriate post-exposure treatment:

- Local treatment of wounds; reducing the rabies virus at the site of bite by washing the wound using of soap and water for 15 minutes.
- Rabies Immunoglobulin (RIG); the anti-rabies immunoglobulin provides passive immunity before vaccine takes effect.
- Human anti- rabies vaccines; use of the cell culture vaccines based on the management guidelines will be enhanced.

Pre-Exposure Vaccination:

- Pre-exposure vaccination will be provided to high risk groups including veterinarians, animal handlers and catchers, wildlife wardens, quarantine officers and laboratory staff handling the virus and potentially infected material.

Training health workers on proper dog bite wound cleaning and management and Continuous education of health professionals on proper dog bite human rabies [7].

Recent Rabies Prevention, Control and Elimination Guiding Principles of the Strategy: Rabies control is a public good (For the benefit or well-being of the public); elimination of human rabies in east Africa is an effort that all interested sectors should be involved in. Rabid domestic dogs transmit at least 98% of human rabies in east Africa. Rabies cycles are maintained by domestic dogs in East Africa; there is no documented evidence that wildlife maintain rabies virus. Sustained annual mass dog vaccination (At least 3 consecutive years) of greater than 70% of dog population eliminates rabies in domestic dogs and subsequently in humans and other domestic animals More than 80% of dogs in Kenya are owned and are accessible for parenteral (by injection) vaccination. Rabies elimination through mass dog vaccination is a cost-effective strategy, saves lives and results in decline in the use of costly human post exposure prophylaxis (PEP) [7].

CONCLUSION

In recent years, rabies is re-emerging and becoming a major public-health problem in all over the world. It is concluded that prompt and state of the art diagnostic tests that are field-based and introduction of efficient national programmes are crucial for the successful control and eradication of rabies. Adequate and appropriate strategies which are based on, One Health? approach are necessary in order to implement efficient control and eradication measures against rabies - endemic, especially in developing countries.

Based on the above conclusion, the following recommendations are given:

- Strict control of free-ranging dogs and mandatory rabies vaccination should be enforced.
- Establishing national animal rabies surveillance network is imperative.
- Post exposure prophylaxis should be decided to initiate or withhold according to postmortem diagnosis of the biting animal.
- The cost of Pre exposure prophylaxis should be decreased or free, especially in rural areas.
- Immediate washing of the wound with soap and water, application of human anti-rabies immunoglobulin and administration of tissue-culture rabies vaccine at 0, 3, 7, 14, 30 and 90 days after exposure.
- To reduce risk for emerging zoonoses, the public should be educated about the risks associated with related to wild and domestic animals and proper surveillance systems should be implemented.
- Use of international law to support the control of communicable diseases.

REFERENCES

1. Rupprecht, C.E., J. Barrett, D. Briggs, F. Cliquet, A.R. Fooks, L.M. McElhinney and D. Horton, 2008. Can Rabies be Eradicated? Developed Biology (Basel), 131: 95-121.
2. Coetzee, P. and L.H. Nel, 2007. Emerging epidemic dog rabies in coastal South Africa: a molecular epidemiological analysis. Virus Res, 126: 186-195.
3. Knobel, D.L., S. Cleaveland, P.G. Coleman, E.M. Fevre and M.I. Meltzer, 2005. "Re-evaluating the burden of rabies in Africa and Asia." Bull World Health Organization, 83(5): 360-368.
4. Belotto, A., L.F. Leanes, M.C. Schneider, H. Tamayo and E. Correa, 2005. Overview of rabies in the Americas. Virus Res., 111: 5-12.
5. Schneider, M.C., A. Belotto, M.P. Ade´, S. Hendrickx, L.F. Leanes, M.J. Rodrigues, G. Medina and E. Correa, 2007. Current status of human rabies transmitted by dogs in Latin America. Cadernos de Sau ´de Pu ´blica, 23: 2049-2063.
6. Bingham, J., 2001. Rabies on Flores Island, Indonesia: is eradication possible in the near future? In: Dodet B, Meslin F-X, Heseltine E, eds. Proceedings of the fourth international symposium on rabies control in Asia, Hanoi, 5-9 March 2001. Montrouge: John Libbey Eurotext, pp: 148-155.
7. Lembo, T., K. Hampson, M.T. Kaare, E. Ernest, D. Knobel, R.R. Kazwala and D.T. Haydon, 2010. The feasibility of canine rabies elimination in Africa: dispelling doubts with data. PLoS neglected tropical diseases,4(2),e626.doi:10.1371/journal.pntd.0000626.
8. Takayama, N., 2008. Rabies: a preventable but incurable disease. Journal of Infectious Chemotheraphy, 14(1): 8-14.
9. Borus, P., 1996. Rabies: the emergence of a microbial threat. East Afr. Med. J., 73(1): 32-34
10. Johnson, N., A. Vos, C. Freuling, N. Tordo, A.R. Fooks and T. Müller, 2010. Human rabies due to lyssa virus infection of bat origin. Veterinary Microbiology, 142: 151-59.
11. Aréchiga Ceballos, N., S. Vázquez Morón, J.M. Berciano, O. Nicolás, C. Aznar López and J. Juste, 2013. Novel lyssa virus in bat, Spain. Emergency Infectious Disease, 19: 793-95.
12. Rupprecht, C.E., R. Willoughby and D. Slate, 2006. Current and future trends in the prevention, treatment and control of rabies. Expert Review. Antiinfective Theraphy, 4(6): 1021-1038.
13. Centers for Disease Control and Prevention. CDC, 1999. Compendium of Animal Rabies Control, 1999; National Association of State Public Health Veterinarians. Morbidity and Mortality Weekly Reports (MMWR), 48(RR-3): 1-9.
14. World Health Organisation, 2000. World Survey of Rabies. WHO Technical Report Series, 34, World Health Organization, Geneva.
15. Fitzpatrick, M.C., K. Hampson, S. Cleaveland, L.A. Meyers and J.P. Townsend, 2012. "Potential for rabies control through dog vaccination in wildlifeabundant communities of Tanzania." PLoS Neglected Tropical Diseases, 6(8): 21.
16. Dacheux, L., O. Delmas and H. Bourhy, 2012. Human rabies encephalitis prevention and treatment: progress since Pasteur's discovery. Biologicals, 40: 61.
17. Fagbami, A.H. and C.K. Ojeh, 1981. Wessclsbron virus infection in West African dwarf sheep: effect of prc-infection serum flavi virus antibodies on severity of disease. Vet. Microbiol., 6: 287-293.
18. Ginger, M., M. Haberl, K.K. Conzelmann, M.K. Schwarz and A. Frick, 2013. Revealing the secrets of neuronal circuits with recombinant rabies virus technology. Front Neural Circuits, 7: 2.
19. Ugolini, G., 2011. Rabies virus as a transneuronal tracer of neuronal connections. Adv Virus Res., 79: 165-202.

20. Yang, J., Q. Li, Y. Gao and J. Wu, 2013. Temporal dependency of multisensory audiovisual integration. In J. Wu (Ed.), Biomedical Engineering and Cognitive Neuroscience for Healthcare, pp: 213-222.
21. Beran, G.W., 1979. Clinical Signs of rabies in dogs. Van Houweling Laboratory, Dumaguete City, Philippines, Unpublished Data.
22. Hemachudha, T., G. Ugolini, S. Wacharapluesadee, W. Sungkarat, S. Shuangshoti and J. Laothamatas, 2013. Human rabies: neuropathogenesis, diagnosis and management. Lancet Neurology, 12: 498-513.
23. Both, L., A.C. Banyard, C. Van Dolleweerd, D.L. Horton, J.K. Ma and A.R. Fooks, 2012. Passive immunity in the prevention of rabies. Lancet Infectious Disease, 12: 397-407.
24. Shankar, S.K., A. Mahadevan, S.D. Sapico, M.S.G. Ghodkirekar, R.G.W. Pinto and S.N. Madhusudana, 2012. Rabies viral encephalitis with propable 25 year incubation period. Annals of India Academy of Neurology, 15: 221-3.
25. Evans, J.S., D.L. Horton, A.J. Easton, A.R. Fooks and A.C. Banyard, 2012. Rabies virus vaccines: is there a need for a pan-lyssavirus vaccine? Vaccine, 30: 7447-54.
26. Mallewa, M., A.R. Fooks, D. Banda, P. Chikungwa, L. Mankhambo and E. Molyneux, 2007. Rabies encephalitis in malaria-endemic area, Malawi, Africa. Emergence Infectious Diseases, 13: 136-39.
27. Fooks, A.R., L.M. McElhinney, D. Horton, D.L. Knobel, S. Cleaveland, P.G.C. Coleman, N. Tordo and T. Müller, 2012. Molecular tools for rabies diagnosis in animals. In: Fooks AR, Müller T, eds. OIE, Compendium of the OIE Global Conference on Rabies Control, pp: 75-87.
28. Lembo, T., M. Niezgoda, A. Velasco-Villa, S. Cleaveland, E. Ernest and C.E. Rupprecht, 2006. Evaluation of a direct, rapid immunohistochemical test for rabies diagnosis. Emergence Infectious Disease, 12: 310-13.
29. Streicker, D.G., S. Recuenco, W. Valderrama, J.G. Benavides, I. Vargas, V. Pacheco, R.E.C. Condori, J. Montgomery, C.E. Rupprecht, P. Rohani and S. Altizer, 2012. Ecological and anthropogenic drivers of rabies exposure in vampire bats: implications for transmission and control. Proceedings of the Royal Society B, 279: 3384-3392.
30. Warrell, M.J. and D.A. Warrell, 2004. Rabies and other Lyssavirus disease. The Lancet, 363: 959-969.
31. Yousaf, Z.M., M. Qasim, S. Zia, M.R. Khan, U.A. Ashfaq and S. Khan, 2012. Rabies molecular virology, diagnosis, prevention and treatment. Journal of Virology, 9: 50.
32. Jackson, A.C., M.J. Warrell, C.E. Rupprecht, H.C. Ertl, B. Dietzschold, M. O'Reilly, R.P. Leach, Z.F. Fu, W.H. Wunner, T.P. Bleck and H. Wilde, 2003. Management of rabies in humans. Clinical Infectious Diseases, 36(1): 60-63.
33. Frenia, M.L., S.M. Lafin and J.A. Barone, 1992. Features and treatment of rabies. Clinical Pharmacy, 11(1): 37-47.
34. Lucas, C.H., F.V. Pino, G. Baer, P.K. Morales, V.G. Cedillo, M.A. Blanco and M.H. Avila, 2008. Rabies control in Mexico. Developed Biology, (Basel), 131: 167-175.
35. Lyles, D.S. and C.E. Rupprecht, 2007. Rhabdoviridae. In: Knipe DM and Howley PM (Editors). Fields Virology, 5th Edition. Lippincott Williams and Wilkins, pp: 1364-1408.
36. Von Teichman, B.F., W.C. De Koker, S.J. Bosch, G.C. Bishop, C.D. Meredith, J. Bingham, 1998. Mokola virus infection: description of recent South African cases and a review of the virus epidemiology. Journal of South Africa Veterinarian Association, 69: 169-171.
37. Sterner, R.T., M.I. Meltzer, S.A. Shwiff and D. Slate, 2009. Tactics and economics of wildlife oral rabies vaccination, Canada and the United States. Emergence Infectious Diseases, 15: 1176-1184.
38. Cliquet, F. and M. Aubert, 2004. Elimination of terrestrial rabies in western European countries. Developments in Biologicals, 119: 185-204.
39. Coleman, P.G. and C. Dye, 1996. "Immunization coverage required to prevent outbreaks of dog rabies." Vaccine, 14(3): 185-186.